Medial HOXA genes demarcate haematopoietic stem cell fate during human development.

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Public Summary:

Scientific Abstract:
Pluripotent stem cells (PSCs) may provide a potential source of haematopoietic stem/progenitor cells (HSPCs) for transplantation; however, unknown molecular barriers prevent the self-renewal of PSC-HSPCs. Using two-step differentiation, human embryonic stem cells (hESCs) differentiated in vitro into multipotent haematopoietic cells that had the CD34(+)CD38(-/lo)CD90(+)CD45(+)GPI-80(+) fetal liver (FL) HSPC immunophenotype, but exhibited poor expansion potential and engraftment ability. Transcriptome analysis of immunophenotypic hESC-HSPCs revealed that, despite their molecular resemblance to FL-HSPCs, medial HOXA genes remained suppressed. Knockdown of HOXA7 disrupted FL-HSPC function and caused transcriptome dysregulation that resembled hESC-derived progenitors. Overexpression of medial HOXA genes prolonged FL-HSPC maintenance but was insufficient to confer self-renewal to hESC-HSPCs. Stimulation of retinoic acid signalling during endothelial-to-haematopoietic transition induced the HOXA cluster and other HSC/definitive haemogenic endothelium genes, and prolonged HSPC maintenance in culture. Thus, medial HOXA gene expression induced by retinoic acid signalling marks the establishment of the definitive HSPC fate and controls HSPC identity and function.